1,110,900

PATENT SPECIFICATION

NO DRAWINGS

1,110,900

Date of Application and filing Complete Specification: 29 April, 1966.

No. 18981/66.

Application made in United States of America (No. 452,916) on 3 May, 1965.

Complete Specification Published: 24 April, 1968.

SEE ERRATA SLIP ATTACHED

Index at acceptance:—A5 B32

Int. Cl.:—A 61 k 7/16

COMPLETE SPECIFICATION

Dentifrice Preparations

ERRATA

SPECIFICATION No. 1,110,900

Page 1, line 26, *for* "references" *read* "reference"

Page 1, line 34, *for* "citric" *read* "citrate"

Page 1, line 45, *for* "odor" *read* "odour"

Page 2, line 60, *for* "aod" *read* "and"

Page 9, Example XV, first column, line 7, *for* "sodium" *read* "Sodium"

THE PATENT OFFICE
22nd May 1968

contains tylosin [illegible]
microbial agent, and a flavouring agent.

Tylosin and desmycosin are antimicrobial macrolides; they are nitrogenous bases which may be employed as such or as the acid-addition salts thereof, and references to the base hereinafter is intended to include such salts.

Examples of useful acid-addition salts of the aforesaid bases include the salts formed with lactic, salicylic, citric, tartaric, gluconic, benzoic, acetic and sulphuric acids, and hydrogen chloride and hydrogen fluoride; i.e., the lactate, salicylate, citric, tartrate, gluconate, benzoate, acetate, sulphate, hydrochloride and hydrofluoride salts. The lactate and tartrate salts are preferred because of their [illegible] character. Tylosin and [illegible] salts are more particularly described, along with methods for their preparation, in United States Patent Specification No: 3,178,341, as well as by McGuire et al. in "Antibiotics and Chemotherapy" 11:320, 1961.

Regular daily use of the dentifrice preparations normally have a pH between 4 and 8, preferably 6 to 7. A buffering system may be employed to maintain a pH within the aforesaid range of 4 to 8 in order to ensure against a reduction in activity of the preparation which may occur under more alkaline or more acid conditions.

Solutions in water of acid salts may be employed in the preparations, or solutions of the free base in aqueous ethanol or other non-toxic solvent, e.g. diethylacetamide and dimethyl sulphoxide. Also, fine suspensions in water, 50% glycerine, aqueous sodium carboxymethyl cellulose, Irish moss or other suitable vehicles may be used.

Any suitable amount of the antimicrobial [illegible] may be incorporated in the dentifrice preparation. The specific amount selected will vary, depending upon the specific type of the preparation and the specific effects desired, but will generally be a minor amount of the preparation, usually at least 0.01% and up to 25% by weight thereof. In the case of dental creams,

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COMPLETE SPECIFICATION

Dentifrice Preparations

We, COLGATE-PALMOLIVE COMPANY, a Corporation organised and existing under the Laws of the State of Delaware, United States of America, of 300 Park Avenue, New York, New York 10022, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to dentifrice preparations containing a certain antimicrobial agent.

The term "dentifrice preparation" as used herein means any preparation intended for application to and/or care of the teeth and/or gums, and includes toothpastes and dental creams, toothpowders, dental lozenges, dental tablets and mouthwashes.

In accordance with the present invention, a dentifrice preparation as hereinbefore defined contains tylosin and/or desmycosin as an antimicrobial agent, and a flavouring agent.

Tylosin and desmycosin are antimicrobial macrolides; they are nitrogenous bases which may be employed as such or as the acid-addition salts thereof, and references to the base hereinafter is intended to include such salts.

Examples of useful acid-addition salts of the aforesaid bases include the salts formed with lactic, salicylic, citric, tartaric, gluconic, benzoic, acetic and sulphuric acids, and hydrogen chloride and hydrogen fluoride; i.e., the lactate, salicylate, citric, tartrate, gluconate, benzoate, acetate, sulphate, hydrochloride and hydrofluoride salts. The lactate and tartrate salts are preferred because of their non-toxic character. Tylosin and desmycosin and their salts are more particularly described, along with methods for their preparation, in United States Patent Specification No: 3,178,341, as well as by McGuire et al. in "Antibiotics and Chemotherapy" 11:320, 1961.

Regular daily use of the dentifrice preparations diminishes mouth odor, prevents and/or arrests gum disease and reduces the formation of tartar and plaque, of calculus and of caries. Notwithstanding these preventative activities in the oral cavity, on complete ingestion of these preparation by test animals in amounts normally used, no evidence has been found of the presence of, or of any systemic action of, the preparations such as in the blood-stream of such animals.

The preparations are beneficial and advantageous in meeting the stringent balance of requirements for effective treatment of oral conditions in that they are stable, they provide for treatment of these conditions at the site thereof, and are safe to use by virtue of the lack of absorption of the antimicrobial agent into the internal body system.

The stability of the preparations is excellent in that they retain useful activity for prolonged periods of time.

The preparations normally have a pH between 4 and 8, preferably 6 to 7. A buffering system may be employed to maintain a pH within the aforesaid range of 4 to 8 in order to ensure against a reduction in activity of the preparation which may occur under more alkaline or more acid conditions.

Solutions in water of acid salts may be employed in the preparations, or solutions of the free base in aqueous ethanol or other non-toxic solvent, e.g. diethylacetamide and dimethyl sulphoxide. Also, fine suspensions in water, 50% glycerine, aqueous sodium carboxymethyl cellulose, Irish moss or other suitable vehicles may be used.

Any suitable amount of the antimicrobial agent may be incorporated in the dentifrice preparation. The specific amount selected will vary, depending upon the specific type of the preparation and the specific effects desired, but will generally be a minor amount of the preparation, usually at least 0.01% and up to 25% by weight thereof. In the case of dental creams,

it is usual to use an amount of 0.01% to 0.5% and preferably 0.02% to 0.3% by weight.

Any suitable substantially water-insoluble polishing agent may be employed in preparations such as toothpastes, powders and creams. There is a relatively large number of such materials known in the art, for example dicalcium phosphate, tricalcium phosphate, insoluble sodium metaphosphate, aluminium hydroxide, magnesium carbonate, calcium carbonate, calcium pyrophosphate, calcium sulphate, bentonite and mixtures thereof. It is preferred to use the water-insoluble phosphate salts as the polishing agents and, more particularly, insoluble sodium metaphosphate and/or a calcium phosphate, such as dicalcium phosphate dihydrate. In general, these polishing agents will comprise a major proportion by weight of the solid ingredients. The polishing agent content is variable, but will generally be up to 95% by weight of the total preparation. In the case of a dental cream, such polishing agents will generally be in the range of 20% to 17%, whereas in toothpowders and dental tablets the polishing agents will usually be in greater proportion, such as 70% to 95%.

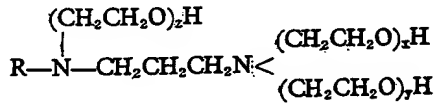
In the preparation of toothpowders, it is usually sufficient to admix mechanically, e.g. by milling, the various solid ingredients, in appropriate quantities and particle sizes.

In dental cream formulations, the liquids and solids are proportioned to form a creamy mass of desired consistency which is extrudable from an aerosol container or a collapsible, e.g. aluminium or lead, tube. In general, the liquids in the dental cream will comprise chiefly water, glycerine, aqueous solutions of sorbitol, propylene glycol, polyethylene glycol 400 or mixtures thereof. It is advantageous usually to use a mixture of water and a humectant or binder such as glycerine or sorbitol. The total liquid content will generally be 20% to 75% by weight of the total preparation. It is preferred in dental creams to use also a gelling agent such as a natural or synthetic gum or gum-like material, e.g., Irish moss, gum tragacanth, sodium carboxymethyl cellulose, polyvinylpyrrolidone or starch, usually in an amount up to 10%, and preferably 0.2% to 5%, of the total preparation.

In other compositions such as mouth rinses the aqueous vehicle may comprise from 20% to as much as 99% of the formulation.

Organic surface active agents used in the preparations may co-act with the antimicrobial agent to achieve increased beneficial activity on oral health and cleanliness, assist in achieving thorough and complete dispersion of the preparations throughout the oral cavity, aod render the preparations more cosmetically acceptable. The organic surface active material may be anionic, nonionic. ampholytic or cationic in nature, and it is preferred to employ as the surface active agent a detergent which imparts to the preparation detersive and foaming properties. Suitable detergents are water-soluble salts of higher fatty acid monoglyceride monosulphates, such as the sodium salt of the monosulphated monoglyceride of hydrogenated coconut oil fatty acids; higher alkyl sulphates, such as sodium lauryl sulphate; alkyl aryl sulphonates, such as sodium dodecyl benzene sulphonate; higher alkyl sulphoacetates; higher fatty acid ester of 1,2-dihydroxy propane sulphonates; and the substantially saturated higher aliphatic acyl amides of lower aliphatic amino carboxylic acid compounds, such as those having 12 to 16 carbons in the fatty acid, alkyl or acyl radicals. Examples of the last mentioned amides are N-lauroyl sarcosine, and the sodium, potassium, and ethanolamine salts of N-lauroyl, N-myristoyl or N-palmitoyl sarcosinates, which should be substantially free from soap or similar higher fatty acid material which tends to reduce the effect of these compounds. The use of these sarcosinate compounds in dentifrice preparations of the present invention is particularly advantageous since these materials exhibit a prolonged and marked effect in the inhibition of acid formation in the oral cavity due to carbohydrates, in addition to exerting some reduction in the solubility of tooth enamel in acid solutions.

Other suitable surface active materials include nonionic agents such as condensates of one mole of sorbitan monostearate with approximately 60 moles of ethylene oxide, and condensates of ethylene oxide with propylene oxide condensates of propylene glycol; and cationic surface active germicides and antibacterial compounds such as di-isobutylphenoxyethoxyethyl dimethyl benzyl ammonium chloride, benzyl dimethyl stearyl ammonium chloride, tertiary amines having one fatty alkyl group (of from 12 to 18 carbon atoms) and two (poly)oxyethylene groups attached to the nitrogen (typically containing a total of from 2 to 50 ethenoxy groups per molecule) and salts thereof with acids, and compounds of the structure



where R is a fatty alkyl group containing from 12 to 18 carbons atoms, and x, y and z total 3 or higher, as well as salts thereof with mineral or organic acids.

It is preferred to use from 0.05 to 5% by weight of the foregoing surface-active materials in the dentifrice preparations.

Various other materials may be incorporated in the dentifrice preparations of the invention. Examples thereof are colouring or whitening agents, preservatives, silicones, chlorophyll compounds and ammoniated materials such as urea, diammonium phosphate and mixtures

thereof. These adjuvants are incorporated in the preparations in amounts which do not substantially affect the properties and characteristics, the adjuvants being selected and used in amounts depending upon the particular type of preparation involved.

For some purposes it may be desirable to include further antibacterial agents in the preparations of the present invention. For example, in combating acid production in the oral cavity the inclusion of twenty parts of N^1 - (4 - chlorobenzyl) - N^5 - (2,4 - dichlorobenzyl) biguanide for each part of the antimicrobial agent may be desirable. Additional antibacterial agents which may be used in amounts ranging from 0.01% to 5% (preferably 0.05% to 1.0%) are, for example, germicidal agents of the guanidine, biguanide, and amine types such as the following: *p*-chlorophenyl biguanide; 4-chlorobenzhydryl biguanide, 4-chlorobenzhydrylguanylurea; N-3-lauroxypropyl - N^5 - *p* - chlorobenzylbiguanide; 1,6-di-*p*-chlorophenylbiguanidohexane; 1-(lauryldimethylammonium) - 8 - (*p* - chlorobenzyldimethylammonium) octane dichloride; 5,6-dichloro-2-guanidinobenzimidazole; N^1-*p*-chlorophenyl-N^5-laurylbiguanide; 5-amino-1,3-bis(2 - ethylhexyl) - 5 - methylhexahydropyrimidine; and their non-toxic acid addition salts.

Any suitable flavouring agent may be employed. The term "flavouring agent" as used herein includes sweetening agents as well as flavours. Examples of suitable flavours include the flavouring oils, e.g., oils of spearmint, peppermint, wintergreen, sassafras, clove, sage, eucalyptus, marjoram, connamon, lemon and orange, as well as sodium methylsalicylate. Suitable sweetening agents include sucrose, lactose, maltose, sorbitol, sodium cyclamate and saccharine. Suitably the flavouring agent may comprise from 0.01% to 5% or more of the preparation.

The preparation of the present invention may also contain a fluorine-containing compound having a beneficial effect on the care and hygiene of the oral cavity, e.g., diminution of enamel solubility in acid and protection of the teeth against decay. Examples thereof include sodium fluoride, stannous fluoride, potassium fluoride, potassium stannous fluoride ($Sn F_2.KF$), sodium hexafluorostannate, stannous chlorofluoride, and sodium monofluorophosphate. These materials which dissociate or release fluorine-containing ions in water, suitably may be present in an effective but non-toxic amount, usually within the range 0.01% to 1% by weight.

The following examples illustrate the invention. The preparations of these examples are prepared in the usual manner using the free base of the antimicrobial agent or salts thereof as indicated. All parts, percentages, amounts and proportions in these examples and elsewhere throughout the specification are by weight unless otherwise specified.

EXAMPLE I

Dental Cream

	Parts
Tylosin lactate	0.1
sodium benzoate	0.15
saccharin	0.20
Sodium lauryl sulphate	1.5
Insoluble sodium metaphosphate	40.6
Dicalcium phosphate dihydrate	5.0
Titanium dioxide	0.4
Stannous fluoride	0.4
Gum tragacanth	1.4
Oil of wintergreen	1.0
Colour	0.03
Water	22.12
Glycerine (99.3%)	27.10

This dental cream is used by brushing the teeth therewith at least once daily.

In the dental cream, the sodium lauryl sulphate may be replaced by sodium-N-lauroyl sarcosinate, and the lactate salt of the antimicrobial agent may be replaced by the hydrochloride salt thereof.

EXAMPLE II

Mouth Rinse	Parts
Tylosin	0.1
Diisobutyl phenoxy ethoxyl ethyl dimethyl benzyl ammonium chloride	0.075
Sorbitan monostearate polyoxyethylene condensate containing about 60 moles of ethylene oxide per mole of the monostearate	0.6
Saccharin	0.035
Ethyl alcohol	14.78
Water	83.87
Colour	0.04
Oil of lemon	0.50

This mouth rinse is used by rinsing the oral cavity with about 10 cc thereof once or more often daily.

In this mouth rinse, the free base of the antimicrobial agent may be replaced by the tartrate salt thereof or by an equal amount of desmycosin.

EXAMPLE III

Chewable Tablet for Brushing	Parts
Insoluble sodium metaphosphate	32.59
Dicalcium phosphate dihydrate	4.03
Poly(ethylene glycol) having a molecular weight of about 6000	5.00
Saccharin	0.25
Sodium carboxymethylcellulose	1.25
Sodium lauryl sulphate	2.25
Starch	3.0
Mannitol	47.3
Talc	0.5
Magnesium stearate	1.25
Flavour and colour	2.48
Tylosin	0.1

The tablet weighs about 0.5 grams and is used by introducing it into the mouth, crushing it between the teeth and then brushing the teeth in the usual fashion with saliva acting as a fluid vehicle for the crushed tablet particles.

EXAMPLES IV and V

Dental Creams

	Example IV	Example V
	Parts	Parts
Sodium saccharinate	0.2	0.2
Sodium benzoate	0.5	0.5
Tetrasodium pyrophosphate	0.25	0.25
Dicalcium phosphate dihydrate	46.75	46.75
Calcium carbonate	5.0	5.0
Sodium carboxymethylcellulose	0.75	0.75
Sodium N-lauroyl sarcosinate	5.71	5.71
Glycerine (99.3%)	23.85	23.85
Oils of peppermint and spearmint, 1:1	0.8	0.8
Water	16.09	16.09
Desmycosin	—	0.1
Tylosin	0.1	—

EXAMPLES VI and VII

Dental Creams

	Example VI	Example VII
	Parts	Parts
Glycerine	27.1	25.286
Irish moss	1.3	—
Saccharin	0.2	0.200
Sodium benzoate	0.15	0.500
Water (deionized)	22.550	14.220
Alumina	—	52.280
Sodium N-lauroyl sarcosinate (35% soln)	—	5.714
Flavour	1.0	0.800
Antimicrobial agent of Example I	0.20	0.100
Sodium carboxymethylcellulose	—	0.900
Sodium lauryl sulphate	1.50	—
Insoluble sodium metaphosphate	45.60	—
Titanium dioxide	0.4	—

These dentifrice preparations are free of calcium containing materials which confer upon them improved ability to diminish calculus formation when used for normal daily brushing of the teeth.

EXAMPLES VIII and IX

Dental Creams

	Examples VIII	Example IX
	Parts	Parts
Glycerine	27.1	27.1
Irish moss	1.3	1.3
Saccharin	0.2	0.2
Sodium benzoate	0.15	0.15
Sodium lauryl sulphate	1.50	1.50
Tylosin	0.075	0.50
Insoluble sodium metaphosphate	40.6	40.6
Anhydrous dicalcium phosphate	5.0	5.0
Titanium dioxide	0.4	0.4
Flavour	1.0	1.0
Water	22.675	22.25

EXAMPLES X and XI

Mouth Rinses

	Example X	Example XI
	Parts	Parts
Ethyl alcohol 95%	14.782	14.782
Flavour	0.218	0.318
Sorbitan monostearate polyethylene condensate containing about 80 moles of ethylene oxide per mole of monostearate	2.500	0.800
Tylosin	0.300	0.020
Glycerine	10.000	10.000
Deionized water	71.590	73.530
Saccharin	0.040	—
Colour (1% soln.)	0.550	0.550
Citric acid monohydrate	0.020	—

EXAMPLES XII—XIV

Chewable Dentifrice Tablets

EXAMPLE XII

	Parts
Dicalcium phosphate dihydrate	76.13
Sodium lauryl sulphate	0.50
Hydrogenated coconut oil monoglyceride sulphate sodium salt	1.20
Diisobutyl phenoxyethoxyethyl dimethylbenzyl ammonium chloride	0.10
Polyethylene glycol 6000	10.00
Arrowroot starch	2.50
Carboxymethylcellulose 7 MP	1.25
Cab-O-Sil (submicroscopic SiO_2)	1.25
Flavour	1.75
Saccharin	0.30
Polyvinyl alcohol (Plasdone)	2.92
Talc	2.00
Tylosin tartrate	0.10

EXAMPLE XIII

	Parts
Magnesium silicate	7.000
Diammonium phosphate	5.000
Monoammonium phosphate	0.500
Urea	3.000
Saccharin	0.300
Flavour	2.500
Tricalcium phosphate	19.100
Calcium carbonate	58.000
Hydrogenated coconut acid monoglyceride sulphate sodium salt	4.500
Tylosin tartrate	0.100

EXAMPLE XIV

	Parts
Magnesium silicate	7.000
Saccharin	0.150
Flavour	2.500
Dicalcium phosphate	85.800
Hydrogenated coconut acid monoglyceride sulphate sodium salt	4.500
Tylosin lactate	0.050

These tablets weigh about 0.5 to 1 gram each and are used by introducing a tablet into the mouth, crushing it between the teeth and then brushing the teeth in the usual manner. The dentifrice particles will tend to be captured by the food-trapping pits, fissures and interproximal areas which are most occlusive of food, thereby collecting in such areas of greatest need.

The antimicrobial agent of Examples XII—XIV may be replaced by equal amounts of the corresponding desmycosin salts.

EXAMPLE XV

Dental Cream

	Parts
Glycerine	12.88
Water	13.38
Sodium lauroyl sarcosinate	2.00
Tylosin	0.20
Irish moss	1.00
Saccharine	0.2
sodium metaphosphate - insoluble	41.85
Dicalcium phosphate - anhydrous	5.0
Titanium dioxide	0.4
Sodium benzoate	0.5
Flavour	0.8
Colour	0.04
Sorbitol (70% solution)	20.00
Hydrated alumina	1.0
Sodium monofluorophosphate	0.75

WHAT WE CLAIM IS:—

1. A dentifrice preparation (as hereinbefore defined) which contains tylosin and/or desmycosin (as hereinbefore defined) as an antimicrobial agent, and a flavouring agent.

2. A preparation as claimed in Claim 1 having a pH of between 4 and 8.

3. A preparation as claimed in Claim 1 or Claim 2 which includes an organic surface-active agent.

4. A preparation as claimed in any of the preceding claims which contains the tartrate salt of the said antimicrobial agent.

5. A preparation as claimed in any of the preceding claims which also contains another antibacterial agent.

6. A preparation as claimed in any of the preceding claims which contains 0.01% to 25% of the said tylosin and/or desmycosin.

7. A preparation as claimed in any of the preceding claims which contains 20% to 95% of a water-insoluble polishing agent.

8. A preparation as claimed in Claim 1 which has a pH of 4 to 8 and which comprises 20% to 99% of an aqueous vehicle, 0.5% to 5% of an organic surface active agent, 0.01% to 5% of a flavouring agent, and 0.01% to 25% of the said tylosin and/or desmycosin.

9. A dentifrice preparation substantially as described in any of the Examples.

KILBURN & STRODE,
Chartered Patent Agents,
Agents for the Applicants.

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